

**REMARKS**

After entry of this amendment, claims 44-66 are pending in this application and presented for examination. Claims 1-43 have been canceled without forfeiting any right to pursue canceled subject matter in a subsequent divisional or continuation application. Claims 44, 51-52, 57-59, 62 and 66 have been amended. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made". All claims pending, including those unchanged by the present amendment, are reproduced below for the convenience of the Examiner.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

The amendments to the claims find support throughout the specification as filed, more particularly on page 10, lines 11-15, wherein the claimed formula and a description of the individual elements and how they are related is set forth. Other amendments are merely to correct minor typographical or grammatical errors.

Applicants believe no new matter has been entered and respectfully request that the amendment be entered.

**I. Formalities**

The Examiner has objected to the disclosure of the instant application for several informalities. Applicants submit herewith a proposed set of amended drawings for approval by the Examiner.

2. The description of Fig. 5 (page 4, lines 9-26) refers only to Fig. 5A - Fig. 5D, while there are Fig. 5A - Fig. 5H. The figures have been amended to correctly reference only Fig. 5A - Fig. 5D.

3. The description of Fig. 8 (page 5, lines 14-22) refers to  $C_{14}^{\circ}$  while Fig. 8 refers to  $C_{13}^{\circ}$ . Fig. 8 has been amended to correctly label the graph as corresponding to  $C_{14}^{\circ}$ .
4. The specification at page 16, line 20, references Fig. 1D, while Fig. 1D is absent from the application. The specification has been amended to correctly refer to Fig. 1C.
5. The specification references Fig. 1E at page 17, line 25, while no Fig. 1E is present in the application. The specification has been amended to remove any reference to Figure 1E.

## **II. Rejections under 35 U.S.C. § 112, 2<sup>nd</sup> Paragraph**

The Examiner has set forth several rejections under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph, which are each addressed in turn below. In response, Applicants amend in part, and respectfully traverse in part.

6. The Examiner has rejected claims 44-66 as allegedly being indefinite for the use of the term “a chemically reactive group.” Claims 44, 52 and 59 set forth that the “chemically reactive group” reacts with the anchoring group that is connected through the linking group to the drug. In order for the “chemically reactive group” to bind to the anchoring group, it must be of a nature to recognize and react with the anchoring group. The nature of the anchoring group, and the nature of the corresponding chemically reactive group to which the anchoring group binds is described in detail in the specification on page 10, line 17 to page 13, line 3. For example, page 12, lines 5-15 sets forth:

Another useful method of linking the active agents of this invention to proteins is through disulfide bonds...A number of reagents are available for chemical modification of cysteine sulfhydryl groups in proteins. One useful group is the thiosulfonates which react rapidly with thiols under physiological conditions... Charged methanethiosulfonate reagents have also been used extensively to elucidate structural features of channel proteins and binding site topology.

The chemically reactive groups needed to react with those functional groups listed above would be clear to a person of ordinary skill in the art. In addition, a person of ordinary skill in the art would know that a protein is simply a polymer of amino acids strung together through peptide bonds, and that as there are only 20 naturally occurring amino acids, the nature of the functionalities on the protein that the anchoring group could then react with, is well-known.

Further, the specification sets forth that the anchoring group must react with a portion of the protein so as not to interfere with the conformational and functional nature of the protein, i.e. the scaffold. Page 6, lines 7-16 of the specification sets forth:

Generally, the scaffolding regions or domains of related proteins have the greatest degree of amino acid sequence diversification. There are at least two reasons for the differences seen in amino acid sequences within the scaffolding region between homologous proteins. First, these scaffolding regions do not commonly overlap structurally with the essential functional domains of the protein (i.e. the active site, phosphorylation domains, allosteric regulatory domains, substrate binding sites, etc.) and therefore changes in amino acid sequence do not affect the active site of the proteins. Second, since scaffolding regions are primarily required for structural support and are generally formed by  $\alpha$ -helices and  $\beta$ -sheet structures, numerous amino acid substitutions are tolerated without major disruption of the overall scaffold structure and without untoward effects on the protein's function.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

7. The Examiner has rejected claims 46, 49, 50, 53, 56-57, 62 and 65-66 as being indefinite because the claims allegedly contain non-elected subject matter. Applicants respectfully point out that the species election was made merely for search purposes under MPEP § 803.02, and in no way limits the scope of the invention to the elected species:

As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D, and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD, or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species...[S]hould no prior art be found that anticipates or renders obvious the elected species, the **search of the Markush-type claim** will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. (emphasis added)

Applicants respectfully point out that no art was found following a search for the elected species, as noted by the Examiner in paragraph 20 of the most recent Office Action. Accordingly, Applicants respectfully request that the rejection be withdrawn, and a full search and examination be done, as Applicants are entitled to.

8. Claim 46 has been rejected by the Examiner as allegedly being indefinite for claiming a drug that does not contain the anchoring group disclosed in claim 44. Applicants respectfully draw the Examiner's attention to the amendments made to claim 44, wherein the anchoring group is more appropriately described as being "linked to" the drug. The drug and the anchoring group are separate entities that are linked, without one being a part of the other. Accordingly, there is no requirement that the drugs disclosed in claim 46 include or describe the anchoring moiety from claim 44. Thus, Applicants respectfully request that the Examiner withdraw the rejection.

9. Claims 47, 54 and 63 have been rejected by the Examiner as allegedly being indefinite because of the use of the term "said biological target molecule is on a protein." In response, Applicants point out that the specification is replete with a description of the preferred protein, and which portions of the protein the anchoring group reacts in order to minimize conformational or functional changes to the protein (e.g. the scaffolding region). (Please see pages 5-6 and 10-13 of the specification, specifically page 6, lines 7-16, discussed above.) Applicants submit that a person of ordinary skill in the art would understand that the anchoring group reacts with an element of the protein that does not interfere with the conformational or functional properties of the protein. While the anchoring group is chosen from a preferred group, each anchoring group can react with a select number of functional groups that are present on the protein, and are chosen from those present on the amino acids of the protein. A person of ordinary skill in the art would recognize the functional groups that are available on the amino acids of the protein, and that are appropriate to react with the selected anchoring group, thus making clear the nature and relation of the biological target molecule to the protein. Accordingly, Applicants respectfully request that the rejection be withdrawn.

10. The Examiner has rejected claims 50, 57 and 66 as being indefinite for containing the allegedly mutually exclusive terms "a dithiopyridyl group, a reactive disulfide". Applicants respectfully point out that USPTO practice permits a Markush group to include both a genus and a species from that genus. MPEP § 2173.05(h) sets forth:

The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily render the scope of the

claim unclear. For example, *the Markush group, "selected from the group consisting of amino, halogen, nitro, chloro and alkyl" should be acceptable even though "halogen" is generic to "chloro."* (emphasis added)

As the inclusion of both a genus and a species in a Markush group is not objectionable according to USPTO patent practice and procedure, Applicants respectfully request that the rejection be withdrawn.

11. Claim 51 has been rejected by the Examiner for allegedly containing language that lacks antecedent basis. In response, Applicants respectfully point out that the preamble of claim 51 has been amended to read "[t]he method in accordance with claim 44, wherein said drug is linked to said anchoring moiety according to the following formula:". This amendment replaces the objectionable term "said compound" with a description that finds support in independent claim 44. In addition, "A" has been redefined more appropriately as "said anchoring moiety" as is consistent with amended claim 44. Accordingly, Applicants respectfully request that the rejection be withdrawn.

12. The Examiner has rejected claim 52 for allegedly lacking antecedent basis for the limitation "with a compound." Under MPEP § 2173.05(e), "[t]here is no requirement that the words in the claim must match those used in the specification disclosure," or that a word must be defined in the preamble. Claim 52 clearly describes in detail what is encompassed by the word "compound" on lines 5-9:

(b) ...said compound comprising (1) A, wherein A is an anchoring moiety and (2) L, wherein L is a linking group, wherein said anchoring moiety reacts with said chemically reactive group of said target molecule to form a covalent bond, thereby resulting in said anchoring moiety being attached to said target molecule through a covalent bond;

Claim 52 has been further amended to clarify that it is the anchoring group and not the drug that reacts with the chemically reactive group of the target molecule:

(d) identifying said drug, D, that forms a covalent bond with said [chemically reactive group]linking group.

Additionally, part (b) of claim 52 clearly sets forth that A-L-D is a compound, and section (d) sets forth that element D, of the compound A-L-D, is a drug. Accordingly, Applicants respectfully request that the rejection be withdrawn.

13. The Examiner has rejected claim 58 as allegedly being indefinite because of the phrase “said biological target molecule comprises a protein target and a bifunctionally chemically reactive group”. Applicants respectfully point that in amended claim 58, the term “bifunctionally chemically reactive group” has been amended to “chemically reactive group”. Consistent with the disclosure on pages 5-6 and 10-13, and as discussed above for claims 47, 54 and 63, a person of ordinary skill in the art would clearly understand the location on the protein and nature of the chemically active group. Accordingly, Applicants respectfully request that the rejection be withdrawn.

14. Claim 59 has been rejected for allegedly lacking sufficient antecedent basis for the terms “on a protein” and “on said protein.” Applicants respectfully submit that a person of ordinary skill in the art would clearly understand that the term “protein” describes a complex molecule consisting of a particular sequence of amino acids (peptides) that are joined to form a protein (polypeptides), and that all proteins consist of carbon, hydrogen, oxygen and nitrogen. In addition, the term “protein” is used throughout the specification, with preferred proteins being discussed on pages 15-25. MPEP § 2173.05(e) sets forth:

A claim term which has no antecedent basis in the disclosure is not necessarily indefinite...A claim is not *per se* indefinite if the body of the claim recites additional elements which do not appear in the preamble.

Applicants submit that the term “protein” is sufficiently defined in the specification, and thus, does not lack antecedent basis. In addition, claim 59 has been amended to clarify the elements of the invention that are a drug. Amended claim 59 discloses that element D, of formula A-L-D, is a “drug”, and that element A is “an anchoring moiety”. Accordingly, Applicants respectfully request that the rejection be withdrawn.

15. The Examiner has rejected claim 65 for reciting the limitation “said anchoring moiety” that allegedly lacks sufficient antecedent basis. Claim 59 has been amended to replace “a first drug” with “an anchoring moiety”, thereby providing the necessary support for the use of the term “said anchoring moiety” in claim 65. Accordingly, Applicants respectfully request that the rejection be withdrawn.

### III. Rejections under 35 U.S.C. § 102(b)/103(a)

The Examiner has rejected claims 44, 47 and 51 under 35 U.S.C. § 102(b), or alternatively under 35 U.S.C. § 103(a), for allegedly being anticipated, or alternatively obvious, in view of Greenfield *et al.* (EP 0398305). The Examiner has further rejected claims 44, 47, 49-52, 54 and 56-58 under U.S.C. § 102(b), or alternatively under 35 U.S.C. § 103(a), for allegedly being anticipated, or alternatively obvious, in view of Pouletty *et al.* (WO 95/10302). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Greenfield *et al.* discloses a drug conjugate containing an antibody or ligand linked anthracycline molecule, wherein only the ligand or antibody of the drug conjugate has specificity for a targeted site. There is absolutely no teaching or suggestion that the anthracycline molecule itself has any specificity to the targeted cells or tissue. The Examiner's attention is respectfully directed to page 10, line 59 to page 11, line 3 of Greenfield *et al.*, wherein it states that the anthracycline molecule enters the cell via the same pathway as if no conjugate were present:

[T]he antibody- or ligand-linked anthracycline molecules...are delivered to the target cells...via the same endocytic pathway that leads to internalization of membrane-bound unconjugated antibodies and ligands.

Moreover, as set forth at page 11, lines 11-12, the drug may be released external to the target cells. Thus, once the ligand or antibody portion of the drug conjugate is anchored, the anthracycline molecule of the drug conjugate does not interact with a specific receptor target, but rather the anthracycline molecule causes *non-selective* tissue damage. Therefore, the invention embodied within Greenfield *et al.* utilizes a drug conjugate with a *single* specific binding moiety that is designed to deliver an anthracycline molecule to produce *non-selective* cytotoxicity. Furthermore, the toxicity generated by the anthracycline molecule need not involve the entity to which the ligand binds.

In stark contrast to Greenfield *et al.*, the present invention teaches a method that is specific for a protein of a particular tissue type, for example, cardiac calcium channels over smooth muscle calcium channels. In addition, claim 44 recites a method utilizing a compound

wherein both the anchor and the drug are specific for a molecular target. In the present invention, once anchored, the drug portion will interact *selectively* with a receptor site on the same protein to which the drug is anchored. Unlike the conjugates in Greenfield *et al.*, that are designed to produce non-specific tissue damage *via* anthracycline-mediated damage and cytotoxicity, claim 44 recites the application of a compound wherein the anchor *and* the drug interact with a selected site on specific target proteins. Therefore, claim 44, and claims dependent there from, are neither anticipated nor rendered obvious in view of Greenfield *et al.* Accordingly, Applicants respectfully request the rejection be withdrawn.

Pouletty *et al.* disclose drug conjugates that bind to a long-lived blood component entity, such as an erythrocyte in circulation. In addition, Pouletty *et al.* discloses conjugates that anchor compounds to the extracellular face of red blood cells, thereby extending their half-life. The sole purpose of the anchoring described in Pouletty *et al.* is to extend the half-life of drugs within the blood. Moreover, the actual delivery of a drug to a molecular target is not specified. There is absolutely no teaching or suggestion in Pouletty *et al.* that the binding of the anchor facilitates the binding of the drug to the same target tissue or protein. As such, the invention of Pouletty *et al.* requires a three-component system: the drug-anchor conjugate; the life-extending entity to which the anchor binds itself; and the target moiety to which the drug binds itself.

Unlike the teaching of Pouletty *et al.*, claims 44, 52 and claims dependent there from, set forth a method utilizing a compound that delivers an active drug to a specific target protein. Once the anchor has bound to the target protein, the binding of the drug is facilitated by the binding of the anchor as a direct result of the juxtaposition of the binding site for the anchor and the binding site for the drug. The binding sites of the anchor and drug are on the same protein and are in close proximity to one another. They are not, however, close enough the anchoring group binding to its target site interferes with the binding of the drug to its separate binding site. Thus, the instant invention discloses a two-component system: the drug-anchor conjugate; and the protein to which both the anchor and the drug bind at two distinct sites. The binding of the drug is not dependent upon the chance encounter with its target within a medium, but rather the target is an integral part of the protein to which the anchor has already attached itself. The Examiner's attention is respectfully directed to Figure 1C, wherein the anchoring



moiety and the drug portion of the molecule are shown binding to the same protein. Applicants submit that it would not have been obvious to take a three-component system as taught in Pouletty *et al.*, and combine the anchor and drug binding sites onto the same structure resulting in a two-component system. In Pouletty *et al.*, the sole purpose of the anchoring described is the extension of the half-life of drugs within the blood. The actual delivery of a drug to a molecular target is not specified. There is absolutely no teaching or suggestion in Pouletty *et al.* that the binding of the anchor facilitates the binding of the drug to the *same* target tissue or protein. As a result, the instant invention is neither anticipated, nor rendered obvious in view of Pouletty *et al.* Accordingly, Applicants respectfully request that the rejection be withdrawn.

#### **IV. Rejections under 35 U.S.C. § 102(e)**

The Examiner has rejected claims 59-62 under 35 U.S.C. § 102(e) for allegedly being anticipated by Fesik, *et al.* (US Patent No. 5,989,827, filed October 31, 1996). Applicants respectfully traverse the rejection.

Fesik *et al.*, teach a process for the design and identification of compounds that bind to a chosen target biomolecule (column 2, lines 33-46). This process comprises the steps of:

1. Identify a first ligand to the target biomolecule;
2. Identify a second ligand to the target biomolecule;
3. Form a ternary complex by binding both ligands to the target biomolecule;
4. Determine the three-dimensional structure of the ternary complex formed; and
5. Link the first and second ligands together to form the drug.

In this process, the two ligands are identified separately from one another, and then linked only in the *step 5* of the process.

In the instant invention, a method is claimed for identifying a drug that binds at a preselected target site on a biological molecules using the following process:

1. Identifying an anchoring moiety that is specific for the first target site on the biological molecule; and

2. Identifying a drug that is specific for said second target site on the biological molecule, wherein the anchoring group and the drug are linked through a linking group.

In contrast to Fesik *et al.*, which teaches first identifying *and then* linking together the binding moieties, the instant invention claims a process of identifying the binding moieties *while* they are linked together by a linking group. Therefore, the linking of the two binding moieties, in the instant invention, took place *prior* to the identification steps. MPEP § 2131 sets forth:

**To anticipate a claim, the reference must teach every element of the claim.**

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). **The elements must be arranged as required by the claim**, but this is not an ipsissimis verbis test, i.e., identity of terminology is not required. In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). (emphasis added)

Since Fesik *et al.* teaches different elements of the claim, i.e. identification *before* linking compared with linking *followed by* identifying, the instant invention is not anticipated.

Additionally, the instant invention teaches a process for discovering a drug that has increasing specificity of the binding of a drug to one species of homologous proteins, i.e. to target the cardiac calcium channel over the smooth muscle calcium channel based on the distinct differences in the proteins (page 23, lines 1-25 of the specification). In contrast, Fesik *et al.* describes a process for discovering a drug that binds to proteins without preference to different tissue types. While Fesik *et al.* deal with only a single protein, the instant invention is able to distinguish homologous proteins belonging to different tissue types.

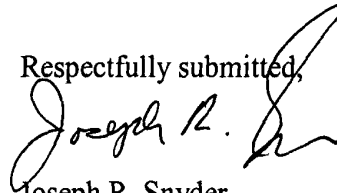
In view of the different method steps in Fesik *et al.* compared with the instant invention, and the ability of the instant invention to bind a drug to a protein specific to a type of tissue while Fesik *et al.* discloses non-selective binding to a protein, Applicants submit that the instant invention is not anticipated by Fesik *et al.* Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at .

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Joseph R. Snyder", with a stylized flourish at the end.

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION**

Page 16, lines 14-20 of the specification:

--Many drugs that modify protein function bind with dissociation constants of  
15 about 100 nM to 10  $\mu$ M. Optimally, the anchoring groups bind the chosen unique domains with  
about 100-fold higher affinity than the drugs bind to their targets. Therefore, the binding affinity  
of the anchoring groups will control localization or binding of the drug to the target protein and  
cell. Because the anchoring group has a much higher binding affinity for its target site, the drug  
portion will be tethered down and allowed to interact dynamically with its target site by  
20 repetitively binding and unbinding as illustrated in **[Figure 1D]**Figure 1C.--

Page 17, lines 20-30 of the specification:

20 --In yet another embodiment, the drug and the anchoring group both contain  
linker domains. These linker domains are then connected via a connecting group. In one  
particular embodiment, the connecting groups do not confer upon the linker domains a direct  
static physical connection between the anchoring group and the drug portion. Specifically, an  
active agent is created by a strong, direct and highly specific interaction within the linking group.  
25 **[See Figure 1E.]** For example, an active agent would comprise the anchoring group attached to  
another group labeled "A" **[in figure 1E]** while the drug portion is comprised of the drug linked  
to a group labeled "B". If "A" and "B" chemically interact, the anchoring group is linked to the  
drug and thereby delivers the drug to the specific target. A number of possible "A-B" pairs exist,  
for example short, digestion-resistant complimentary DNA sequences, lectins and lectin binding  
30 agents, and avidin and biotin agents.--

**IN THE CLAIMS**

1                   44. (Amended) A method for identifying a drug that binds at a preselected  
2 target site on a biological molecule, said method comprising:

3                    providing said preselected target site on a biological target molecule, said  
4                    preselected target site having a chemically reactive group;  
5                    contacting said biological target molecule with a drug **[having]linked to** an  
6                    anchoring moiety specific for said chemically reactive group; and  
7                    identifying said drug **[having]linked to** said anchoring moiety.

1                    **45.**    (Unchanged) The method in accordance with claim **44**, wherein said drug  
2                    having an anchoring moiety is part of a library of compounds.

1                    **46.**    (Unchanged) The method in accordance with claim **44**, wherein said drug  
2                    is a member of the group consisting of a peptide, a peptoid, a random bio-oligomer, a  
3                    benzodiazepine, a hydantoin, a dipeptide, a vinylogous polypeptide, a nonpeptidal  
4                    peptidomimetic, an oligocarbamate, a peptidyl phosphonate, a nucleic acid, an antibody, an  
5                    isoprenoid, a thiazolidinone, a metathiazanone, a pyrrolidine, a morpholino compound, a  
6                    cyclopentane carboxylic acid, phenyalkylamines, dihydropyridines, an antineoplastic agent and a  
7                    local anesthetic.

1                    **47.**    (Unchanged) The method in accordance with claim **44**, wherein said  
2                    biological target molecule is on a protein.

1                    **48.**    (Unchanged) The method in accordance with claim **47**, wherein said  
2                    protein is a member selected from the group consisting of a  $\beta$ -adrenergic receptor, a calcium  
3                    channel, a sodium channel, a potassium channel, membrane transporters and membrane  
4                    receptors.

1                    **49.**    (Unchanged) The method in accordance with claim **44**, wherein said  
2                    anchoring moiety is a member selected from the group consisting of a sulfhydryl-reactive group,  
3                    an alkylating agent and an acylating agent.

1                    **50.**    (Unchanged) The method in accordance with claim **49**, wherein said  
2                    anchoring moiety is a member selected from the group consisting of a methanethiosulfonyl  
3                    group, a dithiopyridyl group, a reactive disulfide, an  $\alpha$ -halo ketone, an  $\alpha$ -diazo ketone, an  
4                    activated ester, a pentafluorophenyl ester, and an anhydride.

1                   **53.**     (Unchanged) The method in accordance with claim **52**, wherein said drug  
2     is a member of the group consisting of a peptide, a peptoid, a random bio-oligomer, a  
3     benzodiazepine, a hydantoin, a dipeptide, a vinylogous polypeptide, a nonpeptidal  
4     peptidomimetic, an oligocarbamate, a peptidyl phosphonate, a nucleic acid, an antibody, an

isoprenoid, a thiazolidinone, a metathiazanone, a pyrrolidine, a morpholino compound, a cyclopentane carboxylic acid, phenylalkylamines, dihydropyridines, an antineoplastic agent and a local anesthetic.

**54.** (Unchanged) The method in accordance with claim **52**, wherein said biological target molecule is on a protein.

**55.** (Unchanged) The method in accordance with claim **54**, wherein said protein is a member selected from the group consisting of a  $\beta$ -adrenergic receptor, a calcium channel, a sodium channel, a potassium channel, membrane transporters and membrane receptors.

**56.** (Unchanged) The method in accordance with claim **52**, wherein said anchoring moiety is a member selected from the group consisting of a sulfhydryl-reactive group, an alkylating agent and an acylating agent.

**57.** (Amended) The method in accordance with claim **56**, wherein said anchoring moiety is a member selected from the group consisting of a methanethiosulfonyl group, a dithiopyridyl group, a reactive **[dissulfide]disulfide**, an  $\alpha$ -halo ketone, an  $\alpha$ -diazo ketone, an activated ester, a pentafluorophenyl ester, and an anhydride.

**58.** (Amended) A method in accordance with claim **52**, wherein said biological target molecule comprises a protein target and a **[bifunctionally]**chemically reactive group.

**59.** (Amended) A method for identifying a drug that binds at a preselected target site on a biological molecule, said method comprising:

identifying **[a first drug]an anchoring moiety** that is specific for a first target site on a protein;

identifying a **[second]** drug that is specific for a second target site on said protein, wherein said **[first drug]anchoring moiety** and said **[second]** drug are linked by a formula

A-L-D

wherein:

9                           A is [a first drug]an anchoring moiety that is specific for a first target  
10 site on a protein;  
11                           L is a linking group; and  
12                           D is a [second ]drug, wherein D is specific for a second target site on said  
13 protein, thereby identifying said drug.

1                   60.   (Unchanged) The method in accordance with claim 59, wherein A is a  
2 member of a combinatorial library of compounds.

1                   61.   (Unchanged) The method in accordance with claim 59, wherein D is a  
2 member of a combinatorial library of compounds.

1                   62.   (Unchanged) The method in accordance with claim 59, wherein said [first  
2 ]drug is a member of the group consisting of a peptide, a peptoid, a random bio-oligomer, a  
3 benzodiazepine, a hydantoin, a dipeptide, a vinylogous polypeptide, a nonpeptidal  
4 peptidomimetic, an oligocarbamate, a peptidyl phosphonate, a nucleic acid, an antibody, an  
5 isoprenoid, a thiazolidinone, a metathiazanone, a pyrrolidine, a morpholino compound,  
6 cyclopentane carboxylic acid, phenylalkylamines, dihydropyridines, an antineoplastic agent and a  
7 local anesthetic.

1                   63.   (Unchanged) The method in accordance with claim 59, wherein said  
2 biological target molecule is on a protein.

1                   64.   (Unchanged) The method in accordance with claim 63, wherein said  
2 protein is a member selected from the group consisting of a  $\beta$ -adrenergic receptor, a calcium  
3 channel, a sodium channel, a potassium channel, membrane transporters and membrane  
4 receptors.

1                   65.   (Unchanged) The method in accordance with claim 59, wherein said  
2 anchoring moiety is a member selected from the group consisting of a sulfhydryl-reactive group,  
3 an alkylating agent and an acylating agent.



1                    66.     (Amended) The method in accordance with claim 65, wherein said  
2     anchoring moiety is a member selected from the group consisting of a methanethiosulfonyl  
3     group, a dithiopyridyl group, a reactive [~~dissulfide~~]disulfide, an  $\alpha$ -halo ketone, an  $\alpha$ -diazo  
4     ketone, an activated ester, a pentafluorophenyl ester, and an anhydride.